Mental Health Series

The "Black Box" Controversy

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The Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee met in September 2004 about the use of antidepressant medications in pediatric patients. The meeting resulted in the committee members voting 15 to 8 recommending the FDA place a "black box" warning label on all antidepressant medications.[1] These two advisory committees determined that "any warning should be extended to all antidepressants for all pediatric use."[2] This black box warning label applies to drugs studied in controlled clinical trials which had findings of increased risk of suicidality in pediatric patients, i.e., Prozac (fluoxetine), Zoloft (sertraline), Remeron (mirtazapine), Paxil (paroxetine), Effexor (venlafaxine), Celexa citalopram), Wellbutrin (bupropion), Luvox (fluvoxamine), and Serozone (nefazodone), as well as other more conventional antidepressants.[3]

HISTORY

The FDA received recommendations from the two advisory committees after review of 24 trials involving over 4,400 pediatric patients from FDA records and documents. The pediatric trials of nine antidepressant drugs prescribed to children and adolescents diagnosed with major depressive disorder (MDD), obsessive compulsive disorder (OCD), or other psychiatric disorders were short-term placebo-controlled trials. The outcome of the trials revealed a "greater risk of an adverse event during the first few months of treatment in those receiving antidepressants."[4] Some of the pediatric trials reviewed are summarized below:

Division of Neuropharmacological Drug Products Review (DNDP) - Dr. Andrew D. Mosholder of the FDA Division of Drug Risk Evaluation spoke to the committee about his analysis. His analysis consisted of a review of GlaxoSmithKline's study of adverse events related to suicide behaviors in pediatric trials of paroxetine as well as the sponsors of eight other drugs (sertraline, venlafaxine, fluoxetine, fluvoxamine, citalopram, nefazodone, mirtazapine and bupropion) who conducted a similar study. He concluded there was a "trend towards an increased attributable risk of suicide-related events" associated with the active drug compared to placebo.[5]

Columbia Suicidality Classification Methodology – Columbia (University) Expert Suicidality Classification Board performed an independent and blinded review of serious adverse events from 25 pediatric antidepressant trials at the request of the FDA. These events included "adverse events categorized by various drug company sponsors as possibly suicide related, accidental injuries, accidental overdoses and all other events categorized by sponsors as serious adverse events." Columbia completed its review and submitted the results to the FDA.[6] Columbia University "suggested a link between antidepressant use and suicidality in the pediatric population."[7]

Treatment for Adolescents with Depression Study (TADS) – The TADS was a randomized clinical trial/controlled study of 439 children, ages 12-17 years old, with the diagnosis of MDD. The study looked at the efficacy of fluoxetine (Prozac) and psychotherapy, Cognitive Behavioral Therapy (CBT). Because of this study, it was estimated that "thirty three (7.5%) of the 439 patients" taking antidepressant "experienced a harm related adverse event" and "twenty-four (5.5%) of 439 patients experienced a suicide-related adverse event."[8]

"BLACK BOX" WARNING

The following is a portion of the text of the "black box" warning which the FDA is requesting to be posted on all labeling of antidepressants for pediatric patients:

Antidepressants increase the risk of suicidal thinking and behavior (suicidality) in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of [Drug Name] or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. [Drug Name] is not approved for use in pediatric patients except for patients with [Any approved pediatric claims here].[4]

The FDA has also prepared precautionary information material for pharmacists to give to patients and has developed medication guides for drugs in this therapeutic class to be included in "unit of use packaging to ensure that every patient receives the Medication Guide."[4]

CONCLUSION

Psychiatric organizations have expressed mixed reviews about the black box warning and its effect on the treatment of children with significant depressive disorders. The American Academy of Child and Adolescent Psychiatry (AACAP) established a Work Group to review its concerns about the FDA's recommendations. The AACAP released a letter to its members on October 31, 2004, stating the "FDA report did not provide data on the benefits of the antidepressants because most of the[9] (sic) antidepressants

tested did not show efficacy compared to placebo." The Work Group did find the warnings "reasonable," and urged AACAP members to continue treating depressed children and adolescents but to explain to the family and patient the information contained in the FDA's new warnings.[9]

The American Psychiatric Association (APA) expressed concern the black box label may frighten families and patients from seeking and receiving needed treatment. However, APA president-elect Steven S. Sharfstein, MD, expressed the view the black box might have a positive impact. Dr. Sharfstein suggested the warning label may allow for more careful monitoring by prescribing doctors and encourage them to spend more time talking to family members about their concerns, uses, and benefits of anti-depressant medication treatments.[10]

To address these concerns, both the APA and AACAP stressed the need for further research to determine both the effectiveness of antidepressants in children and the "precise estimate of the risk of suicidal behaviors or thinking during treatment." In addition, the AACAP stated the consequences of not receiving treatment for childhood depression must be weighed since depression is a serious illness and "interrupts a youth's normal emotional development, undermines self-esteem, interferes with learning in school, undermines friendship with peers and is frequently diagnosed in those who attempt suicide."[11]

Thus a benefit / risk ratio will need to be considered before prescribing antidepressants.■

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